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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,827	01/31/2005	Simona Jevsevar	LB/G-32992A/LEK	2050

72554 7590 07/09/2008

SANDOZ INC
506 CARNEFIE CENTER
PRINCETON, NJ 08540

EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
07/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,827	JEVSEVAR ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☒ Claim(s) *1,6,8-11,13,20,22 and 25* is/are allowed.

6)☒ Claim(s) *2-5,7,15-19,21 and 26* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20080219*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The Information Disclosure Statement (IDS) submitted 19 February 2008 has been entered. Applicant's amendment of the claims filed 7 April 2008 has been entered.

Claims 12 and 23 are cancelled. Claims 25 and 26 have been added. Claims 1-11, 13-22 and 24-26 are pending. Claim 24 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Claims 1-11, 13-22, 25 and 26 are under examination.

Sequence Rules Compliance

The Instant application is not fully in compliance with the sequence rules, 37 CFR 1.821-1.825 for reasons set forth in the previous office action. Briefly, the sequences in Figure 2 and in the specification do not have sequence identifiers. See MPEP§2421.02(d). Applicant has not addressed the issue.

Claim Rejections Withdrawn

The objections to claims 1, 3, 5, 10, 11 and 15-20 for various informalities are withdrawn in response to Applicant's amendment of the claims.

The following rejections under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn in response to Applicant's amendment of the claims:

1) Claim 2, as being indefinite for reciting "the sequence comprises a nucleotide sequence selected from the group consisting of a combination of the following modifications with respect to the native hG-CSF sequence";

2) Claim 2, as being indefinite for reciting "essentially no change";

3) Claim 2, as being indefinite for reciting "in a segment I (or II, or III, or IV)";

4) Claims 4 and 19, as being indefinite for reciting "an expression level of G-CSF, to the total proteins after expression, of at least 50%" without referring to a quantization method;

5) Claim 15, as being indefinite for reciting "applying methods" without defining what methods to apply;

6) Claim 15, as being indefinite for the reciting "a substantial portion"; and

7) Claim 16, as being indefinite for reciting "partial regions".

8) Claims 15-22, as being incomplete for omitting essential steps, i.e., there is an absence of a resolution step which reads back on the preamble of the claimed method;

The rejection of claims 2-4, 7, 15, 17, 19 and 20 under 35 U.S.C. 102(b) as being anticipated by Hockney et al. (U.S. Patent No: 5,840,543), is withdrawn in response to Applicant's amendment of the claims to recite the replacement of CGG Arg148 and GGA Gly150 codons.

The rejection of claims 5, 16, 18, 21 and 22 under 35 U.S.C. 103(a) as being unpatentable over Hockney et al. (U.S. Patent No: 5,840,543), in view of Baneyx et al. (Curr. Opin. Biotech., 1999, 10:411-421), is withdrawn in response to Applicant's

amendment of the claims to recite the replacement of CGG Arg148 and GGA Gly150 codons.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for referring nucleotide positions without referring a SEQ ID for reasons set forth in the previous office action.

Applicant argues that the individual codons in each of sequence segments I-IV which are modified from the native hG-CSF gene sequence are specifically set forth, defined, and enumerated on pages 9-10 of the specification. Applicant argues that it has not been shown that a person having ordinary skill in the art would be unable to do so here with respect to the noted limitations of segments I-IV of claim 2.

Applicants' argument has been fully considered but has not been found to be persuasive.

The specification defines the term "hG-CSF" on pp. 6, as "human granulocyte-colony stimulating factor, comprising the recombinant hG-CSF obtained by the expression in *E.coli*". A search for human G-CSF (also named CSF3) sequence in the Uniprot hits a molecule "P09919" (CSF3 human), which has a signal peptide of 29 amino acids long (positions 1-29), and a G-CSF chain of 178 amino acids long

(positions 30-207) (see attached Uniprot data sheet). The amino acid residues 148 and 150 are not Arg148 and Gly150 as recited in the instant claims. In addition, human G-CSF has three different isoforms a, b and c (they are all naturally occurring hG-CSF). These isoforms have different lengths either in the full length protein or in the mature polypeptides (see attached NCBI protein sequence data sheet), and again, the amino acid residues 148 and 150 in these isoforms are not Arg148 and Gly150 as recited in the instant claims. Therefore, the nucleotide/codon positions would vary depends on which sequence they are referring to.

New Grounds of Objections/Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-5, 7, 15-19 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a modified DNA sequence encoding hG-CSF, a plasmid comprising same, and a process of expressing same, comprising a nucleotide sequence having at least the following sequence segments, modified with respect to a native sequence coding for hG-CSF:

a "segment I" (located at the 5' terminal end of the native hG-CSF sequence between nucleotide positions 3 and 194, comprising replacements selected from the group consisting of replacements of *E. coli* rare codons by *E. coli* preference codons, replacements of GC rich regions by AT rich regions, and combinations thereof;

a "segment II" (located between nucleotide positions 194 and 309 of the native hG-CSF sequence), comprising replacements of *E. coli* rare codons by *E. coli* preference codons;

a "segment III" (located between nucleotide positions 309 and 467 of the native hG-CSF sequence), comprising replacement of a CGG Arg148 codon with a CGT Arg148 codon and replacement of a GGA Gly150 codon with a GGT Gly 150 codon; and

a "segment IV" (located at the 3' terminal end of the native hG-CSF sequence, between nucleotide positions 467 and 536), comprising replacements of *E. coil* rare codons by *E. coli* preference codons;

wherein the DNA sequence further comprises a 5'-UTR of the native hG-CSF sequence; wherein the DNA sequence provides an expression level of G-CSF, to the total proteins after expression, of at least 50% in an expression system, as quantifled by staining protein bands after separation by SDS-PAGE.

What applicant has described in the specification is a synthetic gene (Fopt5) coding for hG-CSF which has the nucleotide sequence set forth in SEQ ID NO: 1. Applicant describes that Fopt5 is codon-optimized by replacing a number of *E. coli* rare

codons with *E. coli* preference codon throughout the gene (i.e., in the four segments of the gene). Applicant describes on pages 9-10 the codon changes at specific positions. Applicant describes that the synthetic Fopt5 gene, when expressed in *E.coli*, yield hG-CSF more than 40% in total protein (pp. 19, Table 1, and pp. 21, Table 2). Applicant, however, has not described other synthetic hG-CSF genes that can produce high yield protein, i.e., more than 50% of total protein. Even though the specification listed codon positions that can be optimized, however, there is no sufficient teaching regarding changes in which codon positions are required and sufficient to achieve the high yield production. Applicant has provided only one species with definitive structure (SEQ ID NO: 1), which is not sufficient to define the characteristics of all synthetic hG-CSF genes encompassed in the claims. Thus, the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the synthetic hG-CSF gene that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is no sufficient teaching regarding structure/function correlation. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a synthetic hG-CSF gene, Fopt5 as set forth in SEQ ID NO: 1, but not the full scope of the claimed synthetic hG-CSF genes, are adequately described in the disclosure.

Claims 2-5, 7, 15-19 and 26 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: *a synthetic DNA sequence coding for hG-CSF, comprising the nucleotide sequence of SEQ ID NO: 1, wherein the DNA sequence provides an expression level of hG-CSF at least 50% to the total proteins,* does not reasonably provide enablement for other hG-CSF synthetic genes, which comprises various nucleotide changes as recited in claim 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

As set forth above, the claims are broad in that they encompass a large genus of molecules, *i.e.,* synthetic hG-CSF genes that contain replacements of multiple *E. coli*

rare codons with *E. coli* preference codon and replacements of GC rich regions by AT rich regions throughout the gene. The claims require that these genes, when expressed in *E. coli*, can produce hG-CSF at a level >50% of total protein. The specification has disclosed one species, a synthetic hG-CSF gene (Fopt5) as set forth in SEQ ID NO: 1, which is codon-optimized and can achieve a high yield of hG-CSF (> 40% of total protein) (pp. 19, Table 1, and pp. 21, Table 2). The specification, however, does not provide supporting evidence that the genus of synthetic hG-CSF genes can act in a similar manner as Fopt5 to produce the required high protein yield. The specification does not provide sufficient guidance regarding the correlation of structure to function, such as what structural changes are required and sufficient so that these molecules possess the required function. While incorporating silent mutations by using *E. coli* preferred codon usage have been demonstrated to improve the level of heterologous protein expression in *E. coli*, however, codon sequence alterations do not always lead to an increase in the levels of protein expression. For example, Krishna Rao et al. (Mol. Biotechnol., 2008, 38(3):221-32) shows a significant variation of the expression levels for 128 native and codon preference rhG-CSF genes (Table 1). Krishna Rao et al. shows that alterations of codon usage at different positions, as well as N-terminal (2-10 codons) AT content, have a significant impact on the G-CSF expression efficiency. Even though the specification listed codon positions that can be optimized (pages 9-10), however, there is no sufficient teachings regarding which codon changes are required and sufficient to achieve the high yield production. There is no sufficient evidence that any combination of these changes would render the molecule the recited

characteristics. Since the specification does not provide the correlation of structure to function, one of skill in the art would evaluate an extremely large number of non-exemplified synthetic G-CSF genes to determine their effects on expression yield. Thus, undue experimentation would be required for the artisan to make and use the invention as broadly claimed.

Due to the large quantity of experimentation necessary to generate the nearly infinite number of synthetic G-CSF genes recited in the claims and screen same for expression yield, the lack of direction/guidance presented in the specification regarding which structural features are required, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of silent mutation on protein expression efficiency, and the breadth of the claims which encompass a large genus of synthetic G-CSF genes, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites the limitation "IPTG" in claim 20. There is insufficient antecedent basis for this limitation in the claim.

In addition, the terms "at least about" and "less than about" in claim 21 are a relative term which renders the claim indefinite. The terms "at least about" and "less than about" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See MPEP 2173.05(b).

Claim Objections

Claims 2, 14, 16 and 17 are objected to because of the following informalities:

The period in claim 2, line 8, before the word “and combinations”, should be a comma.

Claim 14 has a grammatical error for reciting "An expression system according [to] claim 13, substantially free of an antibiotic". In addition, the word “to” should be added after the word “according”.

The period in claim 16, line 3, before the word “wherein the process”, should be removed.

The period in claim 17, line 3, before the word “relative to”, should be removed.

Appropriate correction is required.

Conclusion

CLAIMS 1, 6, 8-11, 13, 20, 22 AND 25 ARE ALLOWABLE.

CLAIM 14 IS OBJECTED.

CLAIMS 2-5, 7, 15-19, 21 and 26 ARE REJECTED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
June 30, 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646